Brightness Sensitivity and Color Perception as Predictors of Relative Afferent Pupillary Defect

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Purpose. To characterize the relationship between brightness sensitivity and color perception and relative afferent pupillary defect (RAPD) in patients with optic neuropathy.

Methods. The "swinging flashlight test" was used to diagnose RAPD, the degree of which was quantified by neutral density filters, in 325 consecutive patients in a case-control study. A separate examiner, masked to the pupillary findings, then assessed participants for Ishihara color plate reading, brightness sense, and red perception. The latter two were quantified by asking the patient to score (out of 100%) brightness (of a light source) or redness (of an object) of the two eyes relative to each other. Pearson correlation coefficients and receiver operating characteristic (ROC) curves were calculated.

Results. Brightness sense ($r = -0.79$; 95% confidence interval [CI], −0.84 to −0.73; $P < 0.0001$), red perception ($r = -0.73$; 95% CI, −0.79 to −0.65; $P < 0.0001$), and Ishihara color plate reading ($r = -0.68$; 95% CI, −0.79 to −0.66; $P < 0.0001$) were each strongly and highly significantly correlated with the diagnosis and degree of RAPD. Brightness sense and red perception were each able to discriminate almost all the area under ROC for the diagnosis of RAPD (area of 0.99; 95% CI, 0.98–1.00; $P < 0.0001$; area of 0.93; 95% CI, 0.90–0.96; $P < 0.0001$, respectively). Sensitivity and specificity of brightness sense in detection of RAPD were 99% (95% CI, 0.97–1.00) and 95% (95% CI, 0.91–0.98), respectively. The red perception test was only slightly less accurate.

Conclusions. Rapid, simple assessments of brightness sense and color perception provide accurate methods to facilitate the diagnosis of optic neuropathy and may prove to be valuable in screening for optic neuropathy or alternatives to the swinging flashlight test. (*Invest Ophthalmol Vis Sci.* 2007;48: 3616–3621) DOI:10.1167/iovs.06-1076

The diagnosis of optic neuropathy may be missed or delayed because of difficulties in eliciting their hallmark clinical feature: the presence of a relative afferent pupillary defect (RAPD), a sign of unilateral or asymmetric bilateral impairment of the anterior afferent visual pathways.[1,2] The method of choice for detecting an RAPD is the "swinging flashlight test," an objective clinical assessment of optic nerve function that generally requires the expertise of an experienced specialist. Even specialists, however, can struggle to elicit this sign under circumstances of dark irides, and sluggish, dilated, or miotic pupils. Moreover, given that screening for signs of optic neuropathy is often performed by nonmedical staff, there is a need for rapid, simple, alternative ways to help detect RAPD.

We have evaluated the performance of three such methods based on the knowledge that brightness sense and color perception are known to be reduced in people with optic nerve disease. We have standardized existing methods to assess brightness sense, red perception, and color vision and have formally tested each to detect RAPD against the swinging flashlight test.

Patients and Methods

Patients

All participants were assessed at the Neuro-ophthalmology Service at Wills Eye Hospital (Philadelphia, Pennsylvania). Patients with optic neuropathy were eligible to participate as cases if they had a diagnosis of unilateral optic neuropathy, RAPD, no evidence of other posterior segment or retinal disease in the involved eye, and no excluding characteristics (i.e., significant asymmetric media differences or unilateral pseudophakia, retinal or macular pathology, bilateral optic neuropathy, glaucoma, anisocoria greater than 0.5 mm, congenital dyschromatopsia, or visual acuity worse than 20/40 in the unaffected eye). Patients (without those same excluding characteristics) were eligible to participate as controls if they had a neuro-ophthalmological disorder with no evidence of optic nerve disease or retinal disease (e.g., ocular motility disturbance). One hundred ninety-six patients met the criteria to be cases and 129 to be controls.

Testing

Patients underwent full neuro-ophthalmic history and examination, including visual acuity (VA) obtained from an EDTRS-like chart and converted to logMAR, slit lamp assessment of anterior segment, funduscopy, assessment of the pupillary function, brightness sense, red perception, Ishihara color plates (control plate and 10 test plates) and intraocular pressure measurement. Patients underwent pupillary assessments with the swinging flashlight test and grading of the RAPD with neutral density filters by an examiner (PJS) masked to the results of the subjective assessment of optic nerve function. Brightness sense, red perception, and Ishihara color plates were assessed by a separate examiner (HDM) masked to the results of the pupillary testing and patients' diagnoses. All tests were performed through undilated pupils.

The swinging flashlight test was performed in a darkened room; the RAPD was quantified with neutral density filters, as described by Thompson et al.[2] The light source was the Welch-Allen indirect ophthalmoscope set to 6 V (maximum brightness) and approximately 30 cm away from each patient's eyes. The light source was moved back and forth between the two eyes to examine the pupillary response. The depth of the RAPD was quantified by successively placing neutral density filters in front of the eyes without the RAPD to decrease the light stimulus by a known amount until the pupillary constriction between the two eyes was symmetric. The density of the filter(s) required to balance the pupillary responses was recorded in logarithm (log) units. Measurements of RAPD in this study were in steps of 0.3 log

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units, ranging from 0.3 to 2.4 log units. To establish the validity of RAPD grading by a single observer, RAPD was quantified for 20 patients (not included in the study) by both examiners who were masked to each other's findings. Nineteen of 20 patients had the same measurement; the only discordance differed by 0.3 log units.

Tests for subjective assessment of the optic nerve function were performed in the following sequence: Ishihara color plates, red perception, brightness sense. Ishihara color plates were tested in each eye separately while the other eye was occluded. Red perception was assessed using a red top on the tropicamide eyedrop bottle (approximately 20 mm in diameter). Stimulus was presented to each eye separately, approximately 30 cm from the eye tested, and was placed in the center of the patient's visual axis, and the patient was asked to look directly at the tip of the bottle top. During brightness sense assessment, they were asked to look directly into the light.

Patients were also asked whether the bottle top was equally red in both eyes. An affirmative answer ended the test, and the result was recorded as 100% in both eyes. If the patient indicated that the redness of the bottle top differed between the eyes, then the stimulus was re-presented to the eye with normal red perception and the patient was asked, "if the top of the bottle is 100% red (or worth 100 dollars) in this eye, then how many percent is the redness of the bottle top in the other eye (or how much is the redness worth in the other eye)?" The stimulus was presented to each eye for an equal period of time.

Brightness sense was assessed with the indirect ophthalmoscope set at 6 V. Light was shone into one eye, and the patient asked to fixate on it. The light source was held 30 cm from the patient's eye and lined up to be in the center of the visual axis. It was then swung into the other eye for the same length of time. The patient was asked whether the light was of equal brightness in both eyes. An affirmative answer ended the test, and the result was recorded as 100% in both eyes. If the patient indicated that the brightness perception was different between the eyes, the light was shone in the "brighter" eye first and the patient asked, "if the light is 100% bright in this eye (or worth 100 dollars), then how many percent is the brightness in the other eye (or how much is the brightness worth in the other eye)?" During brightness sense and red perception testing, it was confirmed that the patient was tested with eyes in the primary position, with the stimulus (light source or red tropicamide bottle top) positioned in line with the visual axis.

Statistical Analysis

Pearson correlation coefficients were calculated to assess relationships among brightness sense, red perception, Ishihara color plates (correct number of plates read by the eye with the RAPD), and RAPD severity. Receiver operator characteristic (ROC) curves were constructed to determine the accuracy of brightness sense, red perception, and Ishihara color plates as tests predicting the presence of RAPD. Multivariate logistic regression analysis was used to find independent predictors of RAPD from age, VA, brightness sense, red perception, and Ishihara color plates.

The research complied with the Declaration of Helsinki, and informed consent was obtained from all participants.

Results

Mean age of the 196 patients with optic neuropathy (52.4 years; SD, 17.6 years; range, 11–85 years) was similar to that of the 129 controls (54.5 years; SD, 15.7 years; range, 16–89 years; $P = 0.27$). Sixty-two percent ($n = 122$) of the optic neuropathy group and 53% ($n = 69$) of the control group ($P = 0.13$) were women. As expected, mean visual acuity in the optic neuropathy group was 20/80 (range, 20/20 to hand motions), significantly poorer than the mean of 20/25 among controls (range, 20/20 to 20/40; $P < 0.0001$). Figure 1 shows the distribution of RAPD severity in the study population. Mean

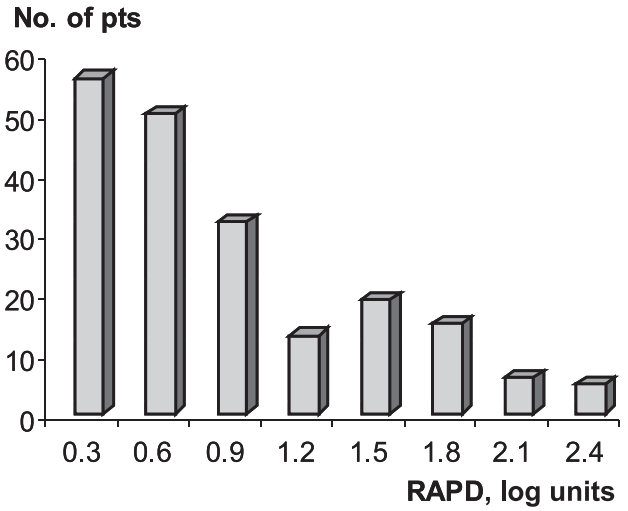

Figure 1. Distribution of RAPD severity in the patient group.

RAPD in the patient group was 0.87 log units (SD, 0.58; range, 0.3–2.4). In the patient group, mean brightness sense (53.7%; SD, 27.4%; range, 1%–100%), mean red perception (60.5%; SD, 32.1%; range, 0%–100%), and mean Ishihara plate score (4.4; SD, 4.1; range, 0–10) were significantly different from those in the control group, for whom the corresponding values were 99.4% (SD, 2.7%; range, 85%–100%) for mean brightness sense, 99.1% (SD, 6.3%; range, 50%–100%) for mean red perception, and 9.7 (SD, 0.9; range, 4–10) for mean Ishihara plate score ($P < 0.0001$).

The difference in distribution of subjective optic nerve function parameters between patients and controls is illustrated as a scatterplot in Figure 2. No control subject had brightness sense lower than 85% ($n = 7$ with altered brightness sense) or red perception lower than 50% ($n = 3$ with altered red perception).

Brightness sense and red perception showed strong and highly significant correlations with RAPD ($r = -0.79$ [95% CI, −0.84 to −0.73; $P < 0.0001$] and $r = -0.73$ [95% CI, −0.79 to −0.65; $P < 0.0001$], respectively; Fig. 3). The correlation coefficient for Ishihara color plates was slightly lower ($r = -0.68$ [95% CI, −0.79 to −0.66; $P < 0.0001$]). The difference between correlation coefficients, however, was not statistically significant (all $P \geq 0.53$). The pattern of data spread for the above suggested the possibility of the exponential decay model, providing a better fit for the data. However, an inspection of residuals coupled with the Akaike information criterion (AIC) goodness-of-fit statistic did not demonstrate a significant advantage of higher-order functions over a liner relationship. Linear R^2 for brightness sense was 0.62, and decay R^2 was 0.64; linear R^2 for red perception was 0.53, and decay R^2 was 0.54; linear R^2 for Ishihara color plates was 0.46, and decay R^2 was 0.51 (all $P < 0.0001$).

Multivariate logistic regression analysis showed that brightness sense ($P < 0.0001$), visual acuity ($P = 0.014$), and age ($P = 0.025$) were the only significant independent predictors of RAPD. However, brightness sense, red perception, and Ishihara color plates were significantly intercorrelated ($r = 0.8$, $P < 0.0001$, for brightness sense and red perception; $r = 0.66$, $P < 0.0001$, for brightness sense and Ishihara color plates; and $r = 0.67$, $P < 0.0001$, for red perception and Ishihara color plates). Hence, red perception and Ishihara color plates were also independent predictors of RAPD. Brightness sense had a stronger correlation with RAPD, but the difference between

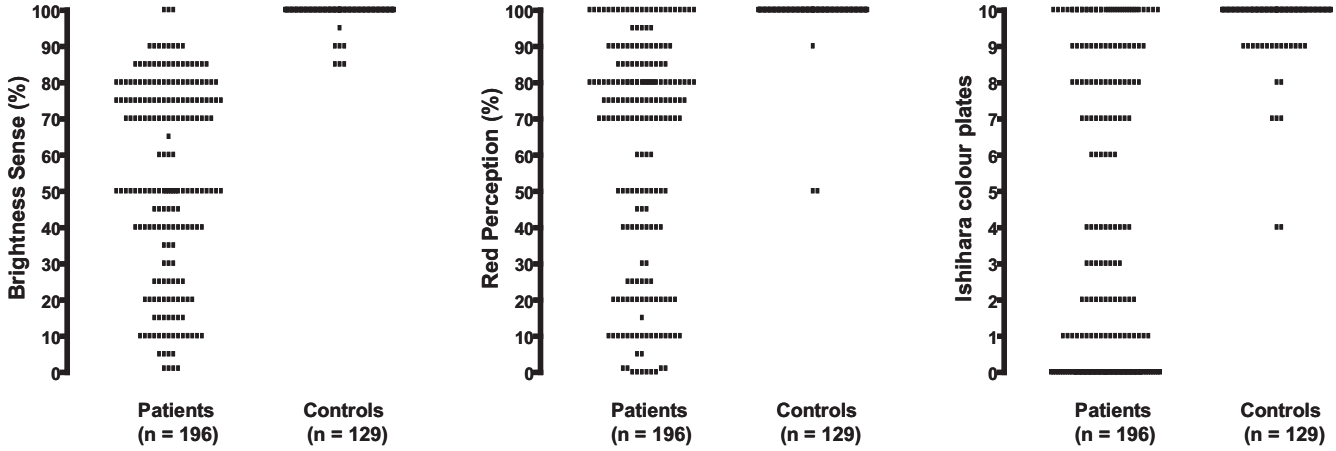

FIGURE 2. Distribution of subjective optic nerve function parameters in patients.

these correlations was not statistically significant. Interchanging one for another in the model did not produce a significant difference. Overall adjusted R^2 for the multivariate regression model was 0.95.

ROC curves were used to assess accuracy of these tests as predictors of RAPD. Values for the area under the ROC (AUROC) curve were 0.99 (95% CI, 0.98–1.00; $P < 0.0001$) for brightness sense, 0.93 (95% CI, 0.90–0.96; $P < 0.0001$) for red perception, and 0.88 (95% CI, 0.84–0.91; $P < 0.0001$) for Ishihara color plates (Fig. 4). Values for the AUROC curve for combinations of tests were 0.99 ($P < 0.0001$) for brightness sense and red perception (Fig. 5), 0.99 ($P < 0.0001$) for brightness sense and Ishihara color plates, 0.96 ($P < 0.0001$) for red perception and Ishihara color plates, and 0.99 ($P < 0.0001$) for all three. The value for the AUROC curve for VA was 0.87 (95% CI, 0.83–0.90; $P < 0.0001$).

When brightness sense was reported to be 90% of normal or worse, sensitivity and specificity were 99% (95% CI, 97%–100%) and 95% (95% CI, 92%–99%), respectively. Red perception had marginally lower values, with a sensitivity of 86% (95% CI, 81%–91%) and a specificity of 98% (95% CI, 95%–100%). Table 1 shows the range of values for brightness sense, red perception, and Ishihara color plates.

When patients in the optic neuropathy group were subdivided according to the severity of RAPD, the mean brightness sense decreased as the severity of the RAPD worsened. In the group with subtle RAPD (0.3 log units), the mean brightness sense was 75.6% (SD, 12.9%); in those with mild RAPD (0.6–0.9 log units), it was 59.5% (SD, 20.4%); in those with moderate RAPD (1.2–1.5 log units), it was 30.9% (SD, 23.0%); and in those with severe defect (>1.5 log units), it was 16.3% (SD, 13.1%). Ishihara color plates did not add significant benefit to the combination of brightness sense and red perception for detecting RAPD. Only two patients had brightness sense of 90% or greater and Ishihara scores of 8 or less. Twenty-five patients had red perception of 90% or greater and Ishihara scores of 8 or less, but, again, only two of them had both brightness sense and red perception equal to or better than 90%.

DISCUSSION

We have demonstrated that rapid, simple tests of brightness sense and red perception are able to detect, the clinical hallmark of optic neuropathy, with a high degree of accuracy. Because these tests can be conducted easily by nonmedical staff, they may prove to be of value in disease screening (thereby helping to reduce the number of missed or delayed diagnoses). Even for specialists, they may be useful adjuncts to the swinging flashlight test under circumstances of miosis, mydriasis, dark irides, iritis, or iris injuries. Our results show that subjective brightness sense and color perception are accurate surrogates for the presence of RAPD and, consequently, that they may be helpful in providing an alternative system to identify and quantitatively grade RAPD, with brightness sense marginally more reliable than the other tests. In addition to high sensitivity (0.99 when brightness sense was reported to be greater than 90% of normal), specificity of 0.95 suggests a low-false negative rate. No control patient reported a bright-

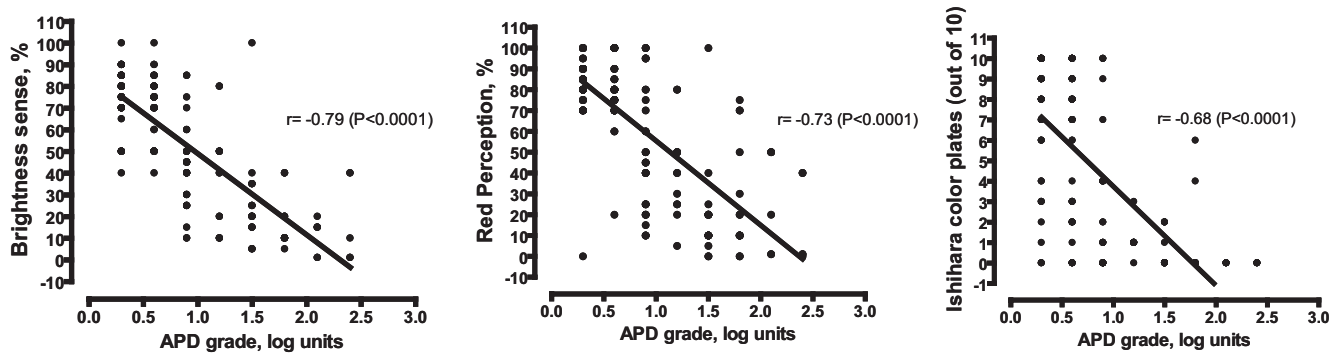

FIGURE 3. Correlation coefficients for the degree of impairment in brightness sense, red perception, Ishihara color plates, and RAPD severity.

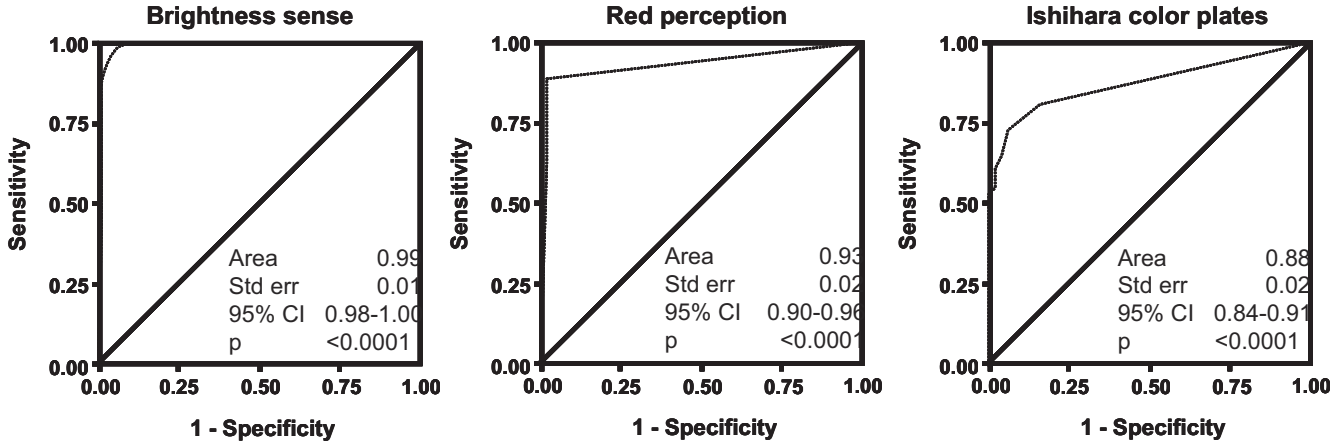

FIGURE 4. ROC curves for brightness sense, red perception, and Ishihara color plates as predictors of RAPD of 0.3 log units or greater in patients with optic neuropathy.

ness sense lower than 85% compared with the fellow eye. Our results suggest that these tests reliably detect RAPD, with the percentage of decrease in sensitivity paralleling the degree of RAPD.

We used a test for brightness sense that does not require dilation of the pupils or specialized equipment. In addition, though we used an indirect ophthalmoscope, any simple source of bright light, such as a torch, could be used instead. By contrast, previous studies of brightness sense have reported lower accuracy in RAPD detection despite methods that involve specialized equipment, including cross-polarizing filters, viewing screens, or computerized devices.[3–7] Lam and Thompson[3] assessed brightness sense in 24 randomly selected patients by asking them to compare the brightness perceived by each eye of a uniformly lit screen 5 feet away with both pupils dilated. Brightness sense was then graded with neutral density filters. The correlation coefficient between brightness sense and RAPD was 0.52. Browning et al.[4] evaluated brightness sense as a predictor for RAPD in 206 patients examined at general ophthalmic, retinal, and neuro-ophthalmology clinics. Brightness sense was tested by asking patients to compare brightness of the light shone sequentially into patients' eyes through closed eyelids. Despite the limitation of this technique—fixation and symmetrical illumination of pupils cannot be guaranteed because of ocular rotation with eyelid closure—brightness sense correctly predicted RAPD presence in 62% of all study patients, in 83% of patients with glaucoma, and in 92% of patients with other optic neuropathies. Other investigators have used cross-polarizing filters[5,6] to show significantly reduced brightness sense among patients with optic neuropathies. Attempts have also been made to develop automated detectors of RAPD with computerized pupillography devices.[8,9] At present, however, the technique is limited in its clinical usefulness in that it requires specific equipment, is unable to identify RAPD of 0.6 log units or smaller with high enough reliability,[8] and has marginal sensitivity.[9]

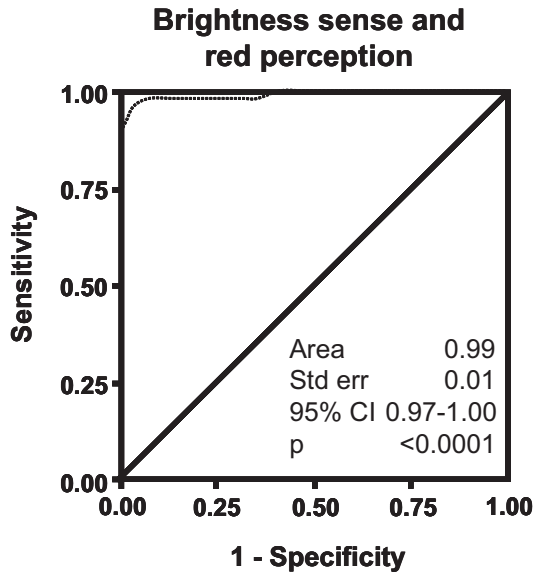

FIGURE 5. ROC curves for combined brightness sense and red perception as a predictor of RAPD in patients with optic neuropathy.

The biological basis for the strong correlation of brightness sense and RAPD lies in the distribution of fibers that subserve pupillomotor responses. The spatial distribution of pupillomotor retinal ganglion cells projecting to the pretectum is thought to be proportional to the distribution of visual retinal ganglion cells projecting to the lateral geniculate nucleus.[10] Furthermore, the magnitude of RAPD has been shown to correlate with the degree of visual field loss.[10–13]

Red perception showed a slightly weaker correlation to RAPD than brightness sense, possibly because patients found it more difficult to quantitate the amount of redness than to grade brightness sensitivity. Another possibility is that certain optic neuropathies preferentially damage one of the opponent channels more than the others and, hence, have a varying effect on the perception of redness. Some investigators[14] have postulated that colors act as dim white stimuli and are thus closer to the visual threshold, rather than a particular effect of the color itself. The lower correlation between Ishihara color plates and RAPD than between the red object and RAPD is probably the result of the fact that it was designed primarily as a screening test for red and green congenital defects. Nevertheless, the test demonstrated good predictive characteristics for the presence of RAPD in our study. Two more important points not studied here must be taken into consideration. One is that the eccentricity of the visual field defect may influence the perception of brightness sense. The other is that more centrally located defects have greater influence on bright-

TABLE 1. Accuracy Parameters for Brightness Sense, Red Perception, and Ishihara Color Plates as Predictors of RAPD in Patients with Optic Neuropathy at Different Cutoff Levels

Cutoff	Sensitivity	Specificity	Likelihood Ratio +ve Test	Likelihood Ratio −ve Test
Brightness sense (%)				
≤95	0.99 (0.97–1.00)	0.95 (0.91–0.98)	18.2 (8.8–39.3)	61.8 (20.1–199.1)
≤90	0.99 (0.97–1.00)	0.95 (0.92–0.99)	21.2 (9.7–43.3)	62.3 (20.3–191.6)
≤85	0.94 (0.91–0.98)	0.98 (0.95–1.00)	40.6 (13.3–124.3)	17.4 (9.8–30.9)
≤80	0.86 (0.81–0.91)	1.00 (1.00–1.00)	—	7.3 (5.1–10.3)
≤75	0.75 (0.69–0.81)	1.00 (1.00–1.00)	—	4 (3.1–5.1)
Red perception (%)				
≤95	0.88 (0.84–0.93)	0.98 (0.95–1.00)	37.95 (12.4–116.3)	8.3 (5.7–12.2)
≤90	0.86 (0.81–0.91)	0.98 (0.95–1.00)	36.86 (12.6–112.9)	6.8 (4.8–9.6)
≤85	0.79 (0.73–0.84)	0.98 (0.96–1.01)	50.68 (12.8–200.9)	4.6 (3.5–6.0)
≤80	0.73 (0.67–0.79)	0.98 (0.96–1.01)	47.06 (11.9–186.6)	3.6 (2.9–.6)
≤75	0.58 (0.51–0.65)	0.98 (0.96–1.01)	37.52 (9.5–149.2)	2.4 (2.0–2.8)
Ishihara color plates				
≤9	0.81 (0.76–0.87)	0.84 (0.77–0.90)	4.98 (3.4–7.4)	4.4 (3.3–6.0)
≤8	0.73 (0.67–0.79)	0.95 (0.91–0.99)	13.45 (6.5–27.8)	3.5 (2.8–4.4)
≤7	0.65 (0.59–0.72)	0.96 (0.93–1.00)	16.85 (7.1–40.0)	2.8 (2.3–3.4)
≤6	0.60 (0.53–0.67)	0.98 (0.96–1.01)	38.50 (9.7–153.0)	2.4 (2.1–2.9)
≤5	0.57 (0.50–0.64)	0.98 (0.96–1.01)	36.53 (9.2–145.3)	2.3 (1.9–2.7)

Values in parentheses are 95% CI.

ness sense. Most of the patients tested in this study had central visual field loss, which explains the very strong correlation with brightness sense.

The potential limitations of this study warrant consideration. Because all optic neuropathies were analyzed together and other potential causes of RAPD (such as large retinal lesions) were excluded, it was not possible to examine the strength of the correlations in subgroups of optic neuropathy or other ocular abnormalities. We excluded patients with anisocoria. A difference of pupil diameter greater than 0.5 mm may have an effect on the brightness sense when pupil diameter is pharmacologically enlarged.[15] Anisocoria may also cause approximately 0.1 log unit RAPD per millimeter of pupil diameter difference.[16] This should be considered in evaluating a patient with a unilateral dilated pupil. We excluded patients with cataracts because other investigators have shown brightness estimates to be unaffected by media change.[6] We also excluded patients with bilateral optic nerve disease. All the patients with optic neuropathy had monocular disease and most had decreased central visual acuity, implying the presence of a central scotoma. Therefore, our findings cannot be directly applied to patients with bilateral optic neuropathy such as glaucoma or pseudotumor cerebri. If the process is symmetrical, patients may not have a difference in brightness sense between the two eyes (just as they may not have relative afferent pupillary defects) despite the bilateral optic neuropathy. Finally, this study was performed in a neuro-ophthalmic clinic with specific inclusion and exclusion criteria. It will be important to evaluate sensitivity and specificity in a general ophthalmic and general medical environment. Although the technique outlined in this study is simple to implement, it does require the examiner to hold the light source in front of both eyes at the same angle to prevent different levels of illumination.

In conclusion, assessments of brightness sense and color perception as described in this study are simple, inexpensive, practical tests with high sensitivity and specificity for RAPD detection. They require little experience with ocular examination and have excellent predictive characteristics for the presence of optic neuropathy. This clinical study has shown that these tests are reliable, valid surrogates for identifying RAPD if swinging flash light test results are ambiguous or an inexperienced examiner has performed the test.

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